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Request for grant of a patent

05SEP02 E746140-1 D02846
P01/7700 0.00-0220644.9

1. Your Reference — NSP/CLD/W657

2. Application number — 0220644.9 — 5 SEP 2002

3. Full name, address and postcode of the or each Applicant

   Country/state of incorporation (if applicable)

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4. Title of the invention — **IMPROVEMENTS IN AND RELATING TO IONTOPHORESIS**

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   Patents ADP number — **190001**

6. Priority claimed to:

Country	Application number	Date of filing
GB	**0216567.8**	**17 July 2002**

7. Divisional status claimed from:

Number of parent application	Date of filing
-	-

8. Is a statement of inventorship and of right to grant a patent required in support of this application? — **YES**

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	12
Claim(s)	3
Abstract	1
Drawing(s)	4 + 4

10. If you are also filing any of the following, state how many against each item

Priority documents	
Translation of priority documents	
Statement of inventorship and right to grant a patent (PF 7/77)	
Request for a preliminary examination and search (PF 9/77)	1
Request for substantive examination (PF 10/77)	
Any other documents (please specify)	

11. We request the grant of a patent on the basis of this application.

Signature: **APPLEYARD LEES**

Date: **04 September 2002**

Appleyard Lees

12. Contact: **Neil Parkinson- 0161 835 9655**

IMPROVEMENTS IN AND RELATING TO IONTOPHORESIS

Field of the Invention

This invention relates to apparatus and methods suitable for iontophoresis.

Background to the Invention

Many processes exist for the safe delivery of drugs or medications to patients. For instance, drugs can be taken in the form of pills, or injected into the body.

Alternatively, and more conveniently, patches placed against the skin can be used to deliver drugs by diffusion through the skin e.g. nicotine patches are popular with people attempting to stop smoking.

Iontophoresis is a process which allows for enhanced transdermal drug delivery by use of an applied current through the skin. The application of an electric current causes the migration of drugs or medications, in their ionic form, into the tissues, the migration being proportional to the electrical charge applied through the iontophoretic system.

Figure 1 shows a schematic diagram of a typical apparatus 10 for providing iontophoresis. The apparatus comprises a current source connected to at least two electrodes 32, 34. The electrodes may be incorporated within a single unit 30, commonly called a transdermal patch.

Typically, one of the electrodes will contain an ionic medication ($D^+ A^-$), and the other an electrolyte ($H^+ A^-$). In use, the electrodes 32, 34 are positioned on the skin 200 of a patient. When a voltage is applied to the electrodes, a circuit is formed between the two electrodes via the body of the patient. The resulting current flowing through the skin 200 of the patient drives the ionic medication into the skin 200 and the tissue 210 to be absorbed by the patients body.

If the electrodes are located within a single unit 30, such as a transdermal patch, then application of both electrodes simultaneously to the skin of the patient can easily be achieved. Further, the electrodes can be located within the unit 30 such that they will be a predetermined distance apart when located on the skin.

The article by Mark R. Prausnitz, "The effects of electric current applied to the skin: A review for transdermal drug delivery", Advanced Drug Delivery Reviews 18 (1996) 395-425, provides an overview of the effects of electrical current applied to skin. The article describes how, at high voltages, the resistivity of the skin may change rapidly. Electrical burns can result if the electric current flowing through tissues or bones is too high. Burns are believed to be due to the highly localised heating by large current densities at sites of low electrical resistance.

In order to prevent such electrical burns, iontophoresis devices utilise a current source 20 to provide a continuous predetermined level of current (e.g. 2mA).

This typically corresponds to an applied voltage of around 2 Volts, and is understood to rarely exceed 10 Volts.

The article by Okabe, Yamaguchi and Kawai, "Iontopheretic Transdermal Administration of the Beta-Blocker Metoprolol", Journal of Controlled Release, 4 (1986) 79-85, describes the application of iontophoresis using a rectangular pulse of 12 Volts at 50kHz. Despite using a relatively high voltage for iontophoresis, the treatment was reported to occur without the development of skin irritation, burning or redness.

It is an aim of embodiments of the present invention to overcome, or at least alleviate, one or more problems of the prior art, whether referred to herein or otherwise.

Statements of the Invention

In a first aspect, the present invention provides an apparatus for providing iontophoresis to a patients body by at least two iontophoresis electrodes at respective locations on the patients body, the apparatus comprising a pulse generating unit connectable to the electrodes, the pulse generating unit being arranged to provide a series of electrical pulses having a peak amplitude of at least 50 Volts.

Preferably, the apparatus further comprises at least two iontophoresis electrodes arranged for connection to said generating unit, for supplying electrical pulses to respective locations on the patients body, at least one of said electrodes incorporating a medication in ionic form for application to the patients body.

Preferably, the width of said pulses lies within the range 1 to 30μs.

Preferably, the apparatus is arranged to deliver said pulses at a predetermined frequency lying within the range 100Hz to 250kHz.

Preferably, said pulses are substantially rectangular in shape.

Preferably, said series of pulses comprises a plurality of spiked pulses.

Preferably, said series of pulses comprises a plurality of bi-polar pulses having a positive voltage peak and a negative voltage peak, the transition time between the positive and the negative peak being at least 70% of the pulse width.

Preferably, said transition time is at least 95% of the pulse width.

Preferably, said pulses have a peak amplitude lying within the range 50 to 450 Volts.

In another aspect, the present invention provides an apparatus for applying an intermittent series of electrical pulses to the body of a patient substantially as described herein with reference to Figures 2 to 5.

In a further aspect, the present invention provides a method for providing iontophoresis to a patient by utilising at least two electrodes at respective locations

on the patients body, at least one of the electrodes incorporating an ionic medication, the method comprising applying a series of pulses, each pulse having a peak amplitude of at least 50 Volts to the electrodes, such that the medication is passed into the body of the patient.

In another aspect, the present invention provides a method for providing iontophoresis to a patient substantially as described herein with reference to Figures 2 to 5.

Brief Description of the Drawings

For a better understanding of the invention, and to show how embodiments of the same may be carried into effect, reference will now be made, by way of example, to the accompanying diagrammatic drawings in which:

Figure 1 is a schematic diagram of a known iontophoresis device in location upon the body of a patient;
Figure 2 illustrates an iontophoresis device in accordance with a preferred embodiment of the present invention;
Figure 3 illustrates a pulse shape in accordance with an embodiment of the present invention;
Figure 4 illustrates an alternative pulse shape in accordance with a further embodiment; and
Figure 5 is a schematic diagram of a circuit suitable for use as a voltage pulse source in the apparatus shown in Figure 2.

Detailed Description of Preferred Embodiments

The currents, and subsequently the voltages, in traditional iontophoresis techniques are limited due to unwanted side effects such as pain, muscle stimulation or thermal burns. However, the present inventors have determined that such problems can be overcome by providing iontophoresis using a pulsed voltage waveform. This allows relatively high voltages to be utilised, without any associated burns or sensations. As the current into the body is non-linear with respect to voltage, this allows a proportionally greater current to be utilised, and subsequently a larger amount of medication to be delivered.

Pulsed voltage signals are utilised in other electro-therapeutic applications such TSE (Tranctuaneous Spinal Electroanalgesia). Appropriate selection of the voltage pulses utilised in delivering iontophoresis may also simultaneously result in the analgesic effects associated with TSE if the iontophoresis pads are located over the spinal column.

Figure 2 illustrates an iontophoresis device 100 in accordance with a preferred embodiment of the present invention. The device is powered by a battery (not shown). Identical reference numerals have been utilised to represent those components that are the same as in Figure 1. As can be seen, the apparatus is essentially the same as the apparatus shown in Figure 1, apart from the fact that instead of a DC current source 20, a pulsed voltage source 120 is utilised to provide a series of voltage pulses to the electrodes 32, 34.

The pulses should have relatively fast rise and fall times so as to minimise the sensations experienced by a patient.

Figure 3 illustrates a pulse stream in accordance with an embodiment of the present invention. Rectangular pulses 130, 132, 134 of width W and amplitude V_p are delivered at regular predetermined intervals T. The pulse frequency is thus 1/T Hz (when T is expressed in seconds). Preferably, the voltage amplitude V_p is greater than 50 Volts, more preferably within the range 50-450 Volts, and even more preferably within the range 100-200 Volts.

Each pulse is preferably of width between 1 and 30μs, and more preferably within the range 4-20μs. The pulse frequency is preferably within the range 100Hz to 250kHz, and more preferably within the range 1kHz to 50kHz.

Whilst in the above embodiment, rectangular shaped pulses have been illustrated, spiked pulses (i.e. pulses with very little signal duration at maximum amplitude) are considered to be particularly effective. Such pulses preferably also have relatively fast rise and fall times. This results in the pulse width W being relatively short compared to the length of the pulse cycle (e.g. W is less than 20% of T, or more preferably W is less than 10% of T, or even less than 5% of T). Spiked pulses are believed to be particularly efficient, as they allow relatively high voltages to be utilised for a given pulse power compared with a rectangular shaped pulse.

Surprisingly, bipolar pulses (i.e. pulses that have both a positive and a negative voltage peak) with a relatively fast transition from zero volts to a first peak in the

pulse, and a relatively fast transition from the final peak in the pulse back to zero volts, but with a relatively gradual transition from the first peak of the pulse to the second peak of the pulse are considered to be extremely effective.

The efficacy of the treatment also appears to be related to the pulse width, with wider pulses providing more effective treatment, presumably due to the increase in the total electrical charge (and hence a greater drug dose) applied to the patient. By utilising bipolar pulses as described above, the pulse width can be increased dramatically compared with the pulse width of a rectangular pulse. For instance, typical rectangular pulses are limited to a width of about 4μs, as longer rectangular pulses lead to a tingling feeling within the patient. However, using bipolar pulses, longer pulse widths can be comfortably utilised on a patient e.g. pulses of widths of up to 30μs, although preferably within the range 10-20μs.

Figure 4 illustrates two such identical bipolar pulse shapes 136, with in this instance the first peak in the pulses being the positive voltage peak. The pulse cycle is of length T_1, with the overall pulse width being W. The peak to peak voltage is shown as V_{pp}, with in this instance both the positive and the negative peaks being of similar amplitude. It will be seen that the pulse can be characterised by three time periods (W_1, W_2, W_3), where $W = W_1 + W_2 + W_3$. The initial transition from zero volts to the first peak voltage (in this case, the rise time of pulse) is of duration W_1, the transition time from the first pulse peak to the second pulse peak is of duration

W_2, and the transition from the second pulse peak back to zero volts is of duration W_3.

It is desirable that W_1 and W_2 are both relatively quick compared with the overall pulse width W i.e. $W_1 + W_3 \leq 0.3W$, and more preferably $W_1 + W_3 \leq 0.95W$. In this example, $W_1 = W_3$. Preferably, the voltage constantly changes during the transition time W_2, and preferably the change is at a constant rate.

Figure 5 illustrates a circuit diagram (utilising standard nomenclature) for a pulsed voltage source 120 in accordance with a preferred embodiment of the present invention. Outputs 121, 122 can each be connected to a respective electrode (or, if more than two electrodes are utilised, respective electrodes). This circuit is suitable for generating both a square wave pulse and a differentiated pulse, depending upon the position of switch S2. If switch S2 is connected to output 121 via capacitor C8 (i.e. in the down position, in the sense the switch is illustrated in Figure 5), then the output will be a differentiated waveform. If the switch S2 is in the other ("up") position, then the output will be a rectangular waveform.

The circuit is preferably powered by a 9 Volt battery, in this instance a PP3 battery 123. The circuit effectively has two separate functions generated by a dual timer micro circuit SE556, 124. The first timer provided by this micro circuit operates to give a fixed frequency and variable time ratio which drives Q1 and T1 to produce about 150V across capacitor C3, the circuit operating as a forward converter. This high voltage is switched through

to the output to get a fast rising pulse. A dummy load could be provided across the output to produce the desired fast fall time of the pulse however, this would waste output power. In order to avoid this wastage of power, whilst still providing a fast rise and fall time, a similar concept to applying a dummy load has been adopted with an active switch ON by Q2 and similar switch OFF when Q3 turns ON.

The duration of the output pulse and the pulse repetition frequency are set by components R5, R6 and C5; no test adjustment is needed, and the cycle is independent of the battery voltage. With component tolerances at ±1%, the pulse width and pulse repetition frequency will be within ± 3% of the desired value.

Table 1 illustrates appropriate values for R5, C5 and R6 for different pulse repetition frequencies (PRF) for a pulse width of 4µs.

Table 1

R5 (Ω)	4k9					1k8		
C5	1nF					2nf		
R6 (Ω)	470K	220K	150K	120K	82K	470K	340K	220K
Pulse Width (µs)	4	4	4	4	4	4	4	4
PRF (µs)	330	153	110	87	61	620	301	460
Freq. (kHz)	3.03	6.54	9.09	11.5	16.4	1.61	3.32	2.17

Appropriate values of the other components are:

R1 = 180R, R2 = 2k2, R3 = 22k, R4 = 3k3, R7 = 15k,
For R5 & R6 see Table 1.

C1 = 100µF, 10V; C2 & C6 = 10nF; C3 = 1µF, 250V; C4 = 680pF, C7 = 4.7nf; C8 = 1nF, 250V

For C5 see Table 1.

LED 1 (Red) HLMP 1700; LED 2 (Green) HLMP 1540

D1, D2, D4, D5 = BAV 20; D3 = HER103,

Q1 = 16N051, Q2 = Zvn120A. Q3 = MPSA92.

ZD1 = BZYX99C5V6

T1 Core, 2xEFD20 +Bobbin +Clips. Prim, 28T, Sec, 650T.

Vr1/S1 = T18A14.103.A.202, (piher).

S2 = 25336NA (APEM)

It will be appreciated that the above description is provided by way of example only, and that various other waveforms, and apparatus suitable for producing such waveforms, would be understood as falling within the scope of the present invention.

Throughout this document, the term patient is not limited to humans, but can be understood as relating to any vertebrate species including mammals. This can include animals such as cats, dogs and horses.

Whilst the preferred embodiment has been described as being powered by a battery, it will be appreciated that any power source could be utilised to power the device, including a power supply comprising a transformer, and suitable for connection to a mains electricity supply.

The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public inspection with this

specification, and the contents of all such papers and documents are incorporated herein by reference.

All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive.

Each feature disclosed in this specification (including any accompanying claims, abstract and drawings), may be replaced by alternative features serving the same, equivalent or similar purpose, unless expressly stated otherwise. Thus, unless expressly stated otherwise, each feature disclosed is one example only of a generic series of equivalent or similar features.

The invention is not restricted to the details of the foregoing embodiment(s). The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

Claims

1. An apparatus for providing iontophoresis to a patients body by at least two iontophoresis electrodes at respective locations on the patients body, the apparatus comprising a pulse generating unit connectable to the electrodes, the pulse generating unit being arranged to provide a series of electrical pulses having a peak amplitude of at least 50 Volts.

2. An apparatus as claimed in claim 1, further comprising at least two iontophoresis electrodes arranged for connection to said generating unit, for supplying electrical pulses to respective locations on the patients body, at least one of said electrodes incorporating a medication in ionic form for application to the patients body.

3. An apparatus as claimed in claim 1 or claim 2, wherein the width of said pulses lies within the range 1 to 30μs.

4. An apparatus as claimed in any one of the above claims, the apparatus being arranged to deliver said pulses at a predetermined frequency lying within the range 100Hz to 250kHz.

5. An apparatus as claimed in any one of the above claims, wherein said pulses are substantially rectangular in shape.

6. An apparatus as claimed in any one of the above claims, wherein said series of pulses comprises a plurality of spiked pulses.

7. An apparatus as claimed in any one of the above claims, wherein said series of pulses comprises a plurality of bi-polar pulses having a positive voltage peak and a negative voltage peak, the transition time between the positive and the negative peak being at least 70% of the pulse width.

8. An apparatus as claimed in claim 7, wherein said transition time is at least 95% of the pulse width.

9. An apparatus as claimed in any one of the above claims, wherein said pulses have a peak amplitude lying within the range 50 to 450 Volts.

10. An apparatus for applying an intermittent series of electrical pulses to the body of a patient substantially as described herein with reference to Figures 2 to 5.

11. A method for providing iontophoresis to a patient by utilising at least two electrodes at respective locations on the patients body, at least one of the electrodes incorporating an ionic medication, the method comprising applying a series of pulses, each pulse having a peak amplitude of at least 50 Volts to the electrodes, such that the medication is passed into the body of the patient.

12. A method for providing iontophoresis to a patient substantially as described herein with reference to Figures 2 to 5.

ABSTRACT

IMPROVEMENTS IN AND RELATING TO IONTOPHORESIS

An apparatus for providing iontophoresis to a patients body by at least two iontophoresis electrodes at respective locations on the patients body. The apparatus comprises a pulse generating unit connectable to the electrodes. The pulse generating unit is arranged to provide a series of electrical pulses having a peak amplitude of at least 50 Volts.

[Figure 2]

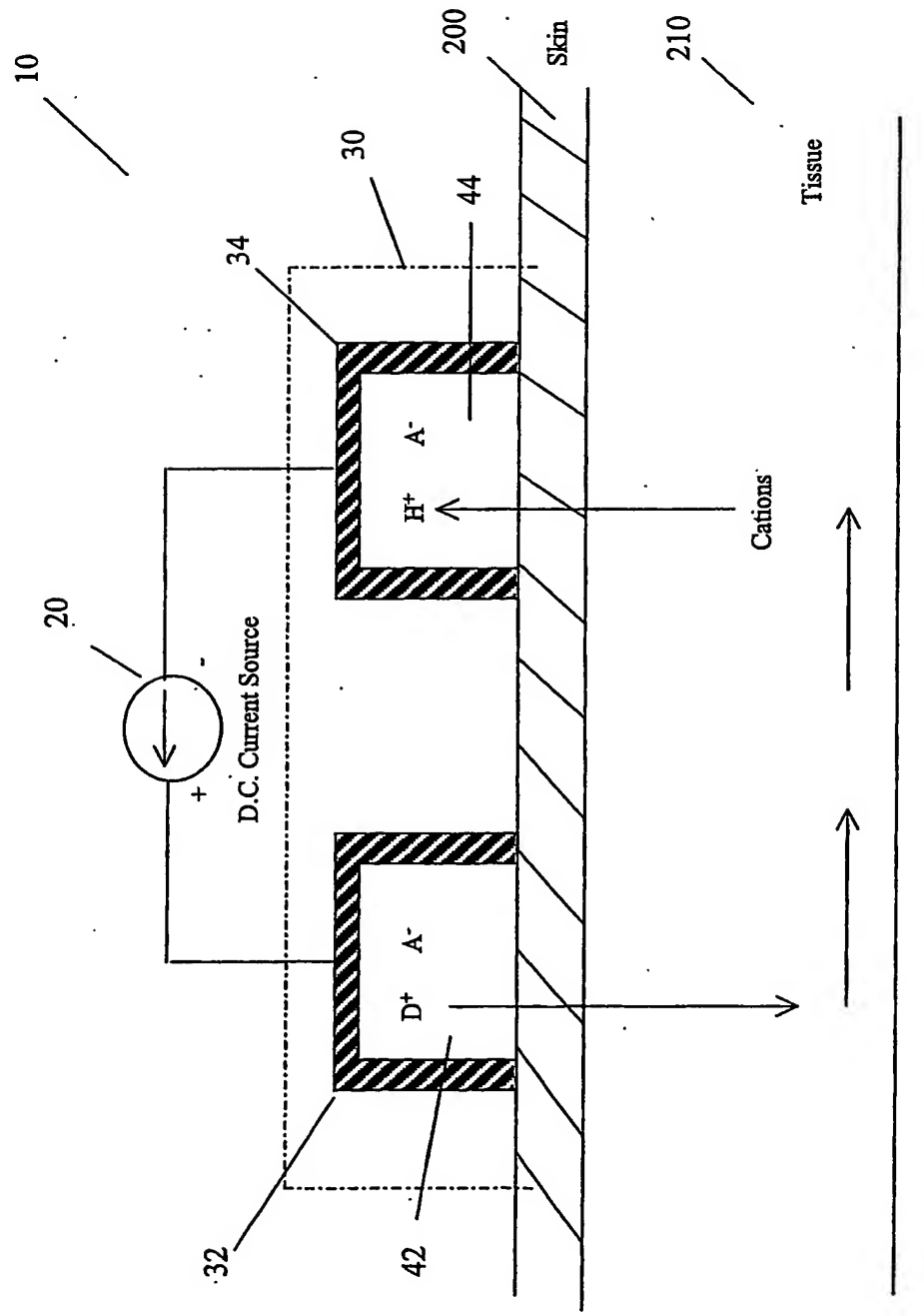
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FIGURE 1

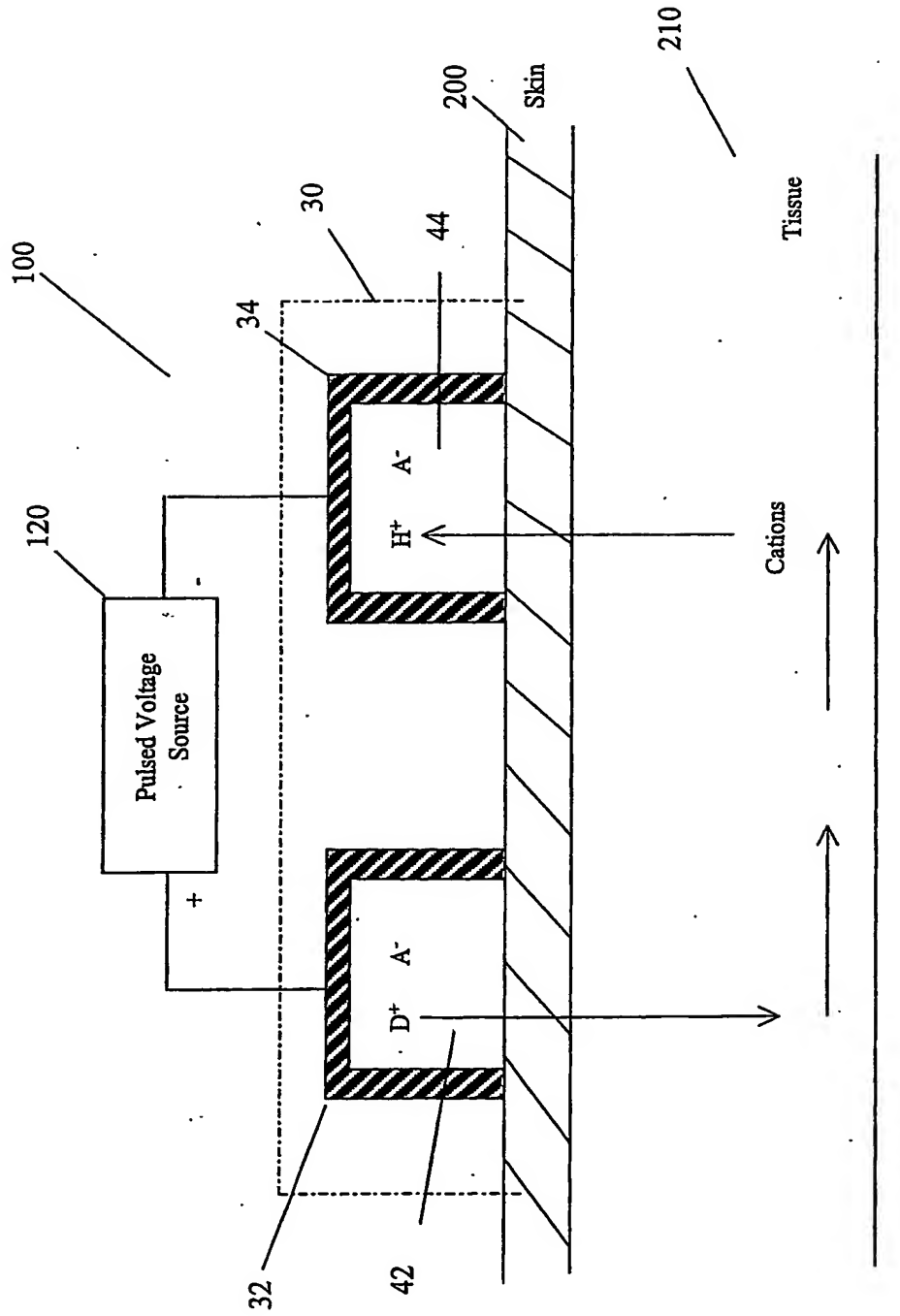
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FIGURE 2

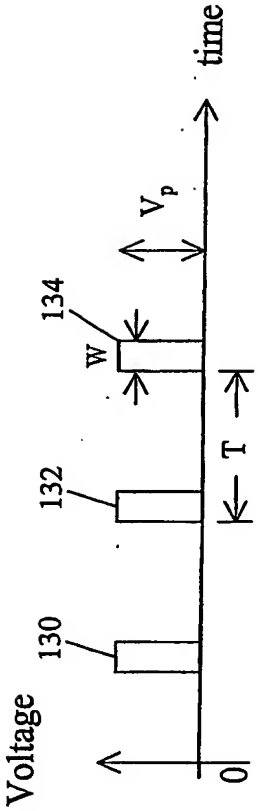


FIGURE 3

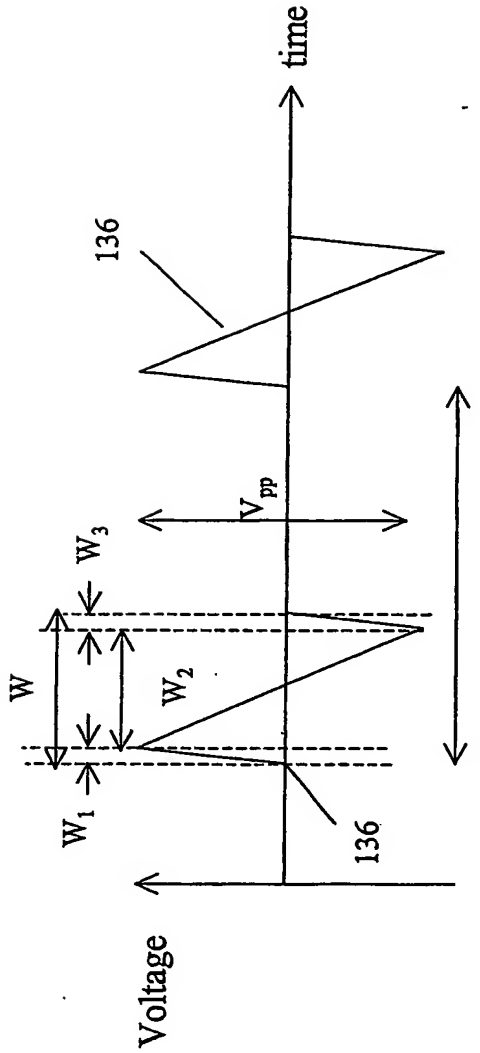
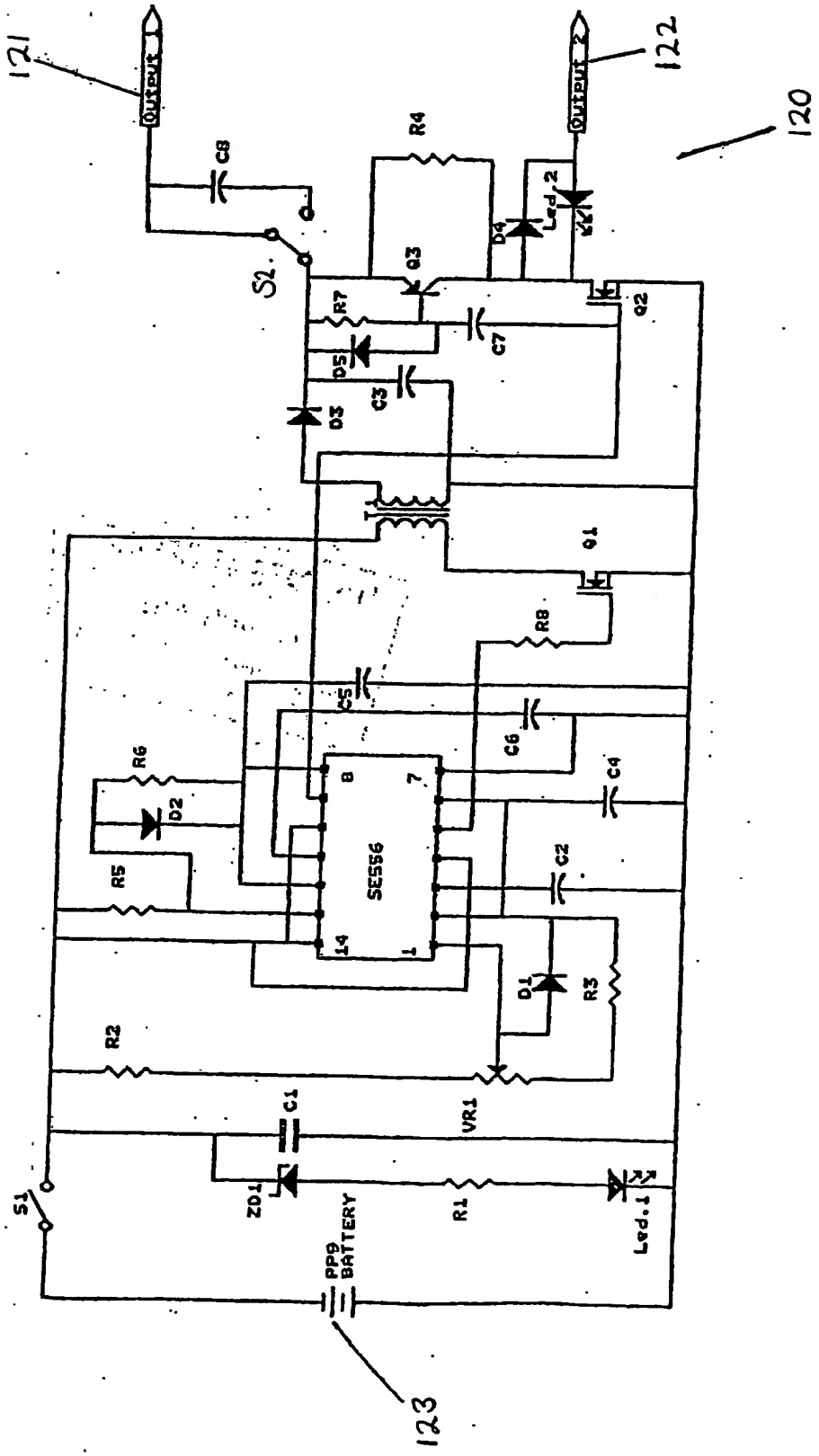


FIGURE 4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D2
R5
SE556
C2
D1
R3
R2
VR1
C1
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Led 1
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PP9 BATTERY
123

FIGURE 5